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EXAMINER	
LANKFORD JR, LEON B	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,933	CLARKE ET AL.	
	Examiner	Art Unit	
	Leon Lankford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-81 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-81 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-47, drawn to a method for inducing the differentiation of insulin-negative cells to insulin-positive cells, classified in class 435, subclass 377.

II. Claims 48-53, 75 and 76, drawn to a composition of insulin-positive cells, classified in class 435, subclass 325.

III. Claims 54-74, drawn to a method of increasing the number of Pdx1-negative cells in a non-adherent sphere of insulin-negative cells, classified in class 435, subclass 384.

IV. Claims 69-74, drawn to a method of disassociating a cluster of cells using Protease XXII, classified in class 435, subclass 378

V. Claims 77-81, drawn to the use of insulin-positive cells in the manufacture of a medicant, classified in class 424, subclass 93.7.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and III-V are each distinct inventions and thus are subject to restriction. The inventions are distinct processes in that the methods are not dependent on each other, not to be used together and have different functions, modes of operation, and effects. In the instant case the method of invention I is directed to a method of differentiating insulin-negative cells to produce insulin-positive cells and requires the resulting insulin-positive cells to be glucose responsive; none of the other methods require a step of culturing an initial population of insulin-negative cells with the intent of producing insulin-positive cells. The method of invention III is directed to a method of increasing the number of Pdx1-negative cells in a non-adherent sphere of insulin-negative cells and requires culture of the spheres in media comprising an FGF mitogen and a cAMP elevating agent for at least one day; none of the other

methods require such culture conditions, nor do they result in an increased number of Pdx1-negative cells. The method of invention IV is directed to a method of disassociating cell clusters using Protease XXII; none of the other methods require use of Protease XXII to disassociate any cell clusters. Finally, the use described in invention V requires manufacture of a medicant; none of the other methods require a step of manufacturing a medicant. Therefore, the methods of inventions I, III, IV and V have distinct methodologies and effects, and one method need not be practiced in order to practice another method; therefore restriction as indicated is proper.

Inventions II and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the insulin-positive cells of invention II are considered to be the product, while the insulin-positive cells of invention II can be made by the method of invention I, insulin-positive cells can alternatively be isolated from a healthy adult human; therefore the product can be made by a materially different process and restriction as indicated is proper.

Inventions II and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the insulin-positive cells of invention II are determined to be the product that can be used in the intended use of invention V; however, insulin positive cells can alternatively be used to secrete insulin in vitro and need not be manufactured into a pharmaceutical composition for administration to a patient. Therefore the product can be used in a materially different process and restriction as indicated is proper.

Invention II is unrelated to inventions III and IV. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the insulin-positive cells of invention II are not capable of being used in the method of invention III, because the method of invention III requires insulin-negative cells. The insulin-negative cells are also not related to the method of invention IV because the method of invention IV is intended to disassociate clusters of cells; there is no disclosed utility between the two inventions, as it is not required the insulin-positive cells be in a cell cluster in need of disassociation.

Furthermore, upon the election of invention I, applicant is required to make the following elections of species so as to define the conditions of a *single* culture method. In situations where the claims call for two or more species, applicants must identify the exact combination of species.

1. **Source of insulin-negative cells** *(must elect a single species)*:

pancreas (claim 3); pancreatic duct tissue (claims 3-5); hepatic or kidney duct or tubule tissue (claims 4 & 5); bile or cystic ducts (claims 4 & 5); tear duct (claims 4 & 5); lactiferous duct (claims 4 & 5); ejaculatory or efferent ducts (claims 4 & 5); seminiferous tubule (claims 4 & 5); lymphatic duct (claims 4 & 5); thoracic duct (claims 4 & 5); embryonic stem cells (claims 10 & 11); fetal stem cells (claims 10 & 11); adult neural stem cells (claims 10-12); adult neural crest stem cells (claims 10-12); adult pancreatic stem cells (claims 3 & 10-12); adult skin-derived stem cells (claims 10-12); adult cardiac stem cells (claims 10-12); adult liver stem cells (claims 10-12); adult endothelial stem cells (claims 10-12); adult hematopoietic stem cells (claims 10-12); adult mesenchymal stem cells (claims 10-12); adult stem cells derived from adult brain tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult spinal cord tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult epidermal tissue (claims 10, 11, 13

and 14); adult stem cells derived from adult dermal tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult pancreatic tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult liver tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult small intestinal tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult large intestinal tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult stomach tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult rectal tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult kidney tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult bladder tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult esophageal tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult lung tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult cardiac muscle tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult skeletal muscle tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult endothelial tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult blood tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult vasculature tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult cartilage tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult bone tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult bone marrow tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult uterus tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult tongue tissue (claims 10, 11, 13 and 14); adult stem cells derived from adult olfactory epithelial tissue (claims 10, 11, 13 and 14).

2. **Specific gp130 agonist present in the culture during selecting step (step (b) of claims 15 and 41*)** *(must elect a single species)* :

cardiotrophin-1 (claims 16 & 41*), LIF (claim 16), oncostatin M (claim 16), IL-6 (claim 16), IL-11 (claim 16), ciliary neurotrophic factor (claim 16), granulocyte colony stimulating factor (claim 16).

3. **Specific mitogen or combination of mitogens present in the culture during the dissociation of the spheres (step (c) of claim 15 and 41*)** *(because claim allows for "at least one mitogen" applicants may elect a combination of one or more species. If a combination is elected all species in the combination must be identified and no alternative language is permitted)*:

FGF-5 (claim 17); FGF-7 (claim 17); FGF-8 (claims 17 & 18); FGF-10 (claim 17); FGF-16 (claim 17); FGF-17 (claims 17 & 18); FGF-18 (claims 17, 18 & 41*); sonic hedgehog (claims 19 & 41*); desert hedgehog (claims 19 & 41*); Indian hedgehog (claims 19 & 41*); an agonist of hedgehog signaling (claim 20); heparin (claims 21 & 42*).

4. **Specific growth factors or growth factor agonists present in the culture during the culture of the spheres (step (d) of claims 15 and 41*)** *(because claims allow for "at least two growth factors or growth factor antagonists" applicants may elect a combination of two or more species. All species in the combination must be identified and no alternative language is permitted):*

FGF-5 (claims 17 & 43*); FGF-7 (claims 17 & 43*); FGF-8 (claims 17, 18 & 43*); FGF-10 (claims 17 & 43*); FGF-16 (claims 17 & 43*); FGF-17 (claims 17, 18, & 43*); FGF-18 (claims 17, 18, 41* & 43*); EGF (claims 22 & 43*); TGF-alpha (claims 22 & 43*); TGF-β (claims 22 & 43*); IGF-I (claims 22& 43*); IGF-II (claims 22& 43*); PDGF (claims 22 & 43*); VEGF (claims 22 & 43*); hedgehog (claims 22 & 43*); heparin (claim 44*).

5. **Material of substratum on which the spheres are plated (step (e) of claims 15 and 41*)** *(a single species must be elected):*

poly-L-ornithin (claims 23 & 45*); laminin (claims 23 & 45*); fibronectin (claims 23 & 45*); superfibronectin (claims 23, 24, 45* & 46*); Matrigel (claims 25 & 47*); a cellular feeder layer (claims 25 & 47*).

6. **Additional factor included in the high-glucose media present during the plating of the spheres (step (e) of claim 15)** *(because the claim allows for "at least one" of the claimed factors applicants may elect a combination of one or more species. All species in the combination must be identified and no alternative language is permitted)*:

serum (claim 28); PYY (claim 28); HGF (claim 28); forskolin (claims 28-31); CPT-cAMP (claims 29 & 31); Na-Butyrate (claims 29 & 31); isobutyl methylxanthine (claims 29 & 31); cholera toxin (claims 29 & 31); 8-bromo-cAMP (claims 29 & 31); dioctanoyl-cAMP (claims 29 & 31); dibutyryl-cAMP (claims 29 & 31); pertussin toxin (claims 29 & 31); prostaglandins (claims 29 & 31); colforsin (claims 29 & 31); β-adrenergic receptor agonists (claims 29 & 31); cAMP analogs (claims 29 & 31); an inhibitor of cAMP phosphodiesterase (claims 29 & 32).

*** Claim 41 and its dependents will only be considered if the exact species recited in claim 41 are elected from the above groups: gp130 agonist must be cardiotrophin-1; combination of mitogens present during disassociation of spheres must be FGF-18 and one of the hedgehog polypeptides; and combination of growth factors present during culture of spheres must include FGF-18.**

Furthermore, upon the election of invention II, applicant is required to make the following elections of species so as to define the conditions of a *single* culture method. In situations where the claims call for two or more species, applicants must identify the exact combination of species.

7. **Additive present in medium used to culture non-adherent spheres (step (b) claim 54)**

FGF-5 (claims 60 & 61); FGF-7 (claims 60 & 61); FGF-8 (claims 60 & 61); FGF-10 (claims 60 & 61); GFG-16 (claims 60 & 61); FGF-17 (claims 60& 61); FGF-18 (claims 60 & 61); CPT-cAMP (claims 60 & 62); forskolin (claims 60 & 62); Na-Butyrate (claims 60 & 62); isobutyl methylxanthine (claims 60 & 62); cholera toxin (claims 60 & 62); 8-bromo-cAMP (claims 60 & 62); dibutyryl-cAMP (claims 60 & 62); dioctanoyl-cAMP (claims 60 & 62); pertussin toxin (claims 60 & 62); prostaglandins (claims 60 & 62); colforsin (claims 60 & 62); β-adrenergic receptor agonists (claims 60 & 62); cAMP analogs (claims 60 & 62); dexamethosone (claims 60 & 63); hydrocortisone (claims 60 & 63); cortisone (claims 60 & 63); prednisolone (claims 60 & 63); methylprednisolone (claims 60 & 63); trimcinolone (claims 60 & 63); betamethasone (claims 60 & 63); follistatin, absent a GLP-1 agonist (claims 64 & 66); follistatin-related gene protein, absent a GLP-1 agonist (claims 64 & 66); an inhibin, absent a GLP-1 agonist (claims 64 & 66); exendin-4, absent a follistatin-based factor (claims 64 & 67); exendin-3 absent a follistatin-based factor (claims 64 & 67); GLP-1 absent a follistatin-based factor (claims 64 & 67); a GLP-1 analog absent a follistatin-based factor (claims 64 & 67); follistatin and exendin-4 (claims 65-67); follistatin and exendin-3 (claims 65-67); follistatin and GLP-1 (claims 65-67); follistatin and a GLP-1 analog (claims 65-67); a follistatin-related gene protein and exendin-4 (claims 65-67); a follistatin-related gene protein and exendin-3 (claims 65-67); a follistatin-related gene protein and GLP-1 (claims 65-67); a follistatin-related gene protein and a GLP-1 analog (claims 65-67); an inhibin and exendin-4 (claims 65-67); an inhibin and exendin-3 (claims 65-67); an inhibin and GLP-1 (claims 65-67); an inhibin and a GLP-1 analog (claims 65-67).

In each of the above groupings of species the species are determined to be sufficiently distinct so that a search and examination of all species in a single patent application would result in a great undue burden on the examiner. The species are determined to be distinct because none is rendered obvious by the others in its group and because the disclosure does not connect them by any design, operation, or

effect. See M.P.E.P. § 806.04(b). A requirement for restriction is permissible if there is a patentable difference between the species as claimed and there would be a serious burden on the examiner if restriction is not required. See M.P.E.P. § 808.01(a). In this case, considering enablement, utility, and description issues for each claimed species, as well as conducting a thorough search of the prior art for each and every combination embodied by the present claims, would pose a serious burden to the examiner.

The examiner wishes to point out for the record that an election of species requirement is for search purposes only and does not necessarily narrow the scope of patentable claims, since all nonelected species are rejoined at the time of allowance. See 37 C.F.R. §1.146 and M.P.E.P. § 809.02(c) for a discussion of species election practice. In short, electing one species does not preclude consideration of the nonelected species later in the prosecution, *i.e.* at the time of allowance. The fact that all of the original claims were generic was the precise reason for the requirement for species election; in the interest of expedient processing of applications, the examiner concentrates on the patentability of the entire invention as it pertains to one species. Once the invention *per se* is claimed in an allowable manner, all disclosed species are rejoined to the claims.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species from each of the appropriate groups listed above, even though this requirement is traversed. Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic

claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

LEON B. LANKFORD, JR.
PRIMARY EXAMINER